REMARKS/ARGUMENTS

Claims 20-22, 24, 31, 34, and 36 have been amended solely to advance prosecution. Applicants expressly reserve the right to reinstate these claims or to file a continuation application or to take other such appropriate action to seek protection of the subject matter encompassed by the previously presented claims.

Specifically, independent claims 20 and 31, and newly independent claim 36, have been amended to recite administration of human interleukin-2 (IL-2) or biologically active variant thereof, where the variant has the ability to promote natural killer (NK) cell expansion and function and has an amino acid sequence having at least 90% sequence identity to the amino acid sequence for human IL-2. Support for recitation of human IL-2 resides in the specification, for example, at page 14, line 1, and page 15, line 28; and support for recitation of biologically active variants of this protein resides throughout the specification, for example, at page 14, line 3, continuing through page 19, line 12. Support for promotion of NK cell expansion and function as the IL-2 activity of interest resides in the specification, for example, at page 1, lines 23-24, at page 3, lines 22-25, at page 28, lines 27-29, and at page 31, lines 23-27. Support for variants having at least 90% sequence identity to the amino acid sequence for human IL-2 resides in the specification, for example, at page 15, lines 24-31, as well as in original claims 27 and 41.

Independent claims 20 and 31 have been amended to recite daily subcutaneous administration of IL-2 or variant thereof. Support for this amendment resides in the original claims and in the specification, for example, at page 12, lines 19-27, at page 28, lines 21-30, and page 29, lines 20-26. Claims 20 and 31 have also been amended to recite a dosing range of 3 mIU/m^2 to 6 mIU/m^2 for IL-2 or biologically active variant thereof. Support for this amendment resides in the specification, for example, at page 11, lines 24-25, and in the dependent claims, for example, claims 22 and 34. Accordingly, claims 22 and 34 have been amended to depend from their respective base claims (i.e., 20 and 31) and to remove the phrase "and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from 3 mIU/m^2 to 6 mIU/m^2". Dependent claims 21 and 24 have been amended to recite 3.5 mIU/m^2 as the dose of IL-2 or biologically active variant thereof. Support for this therapeutically effective dose resides

in the specification, for example, at page 12, line 1. In view of the amendment to claim 31 to recite daily subcutaneous administration, former dependent claim 36 has been rewritten in independent form. No new matter is added by way of claim amendment. Therefore entry of these claim amendments into the above-identified application is respectfully requested.

Applicants wish to remind the Examiner of U.S. Continuation-in-Part Application No. 10/293,664, filed November 12, 2002, and published as U.S. Patent Application Publication No. 2003-0185796, which is referred to in the comments provided herein below, and for which prosecution on its merits is forthcoming.

Claims 20-24, 26, 28-38, 40, and 42-44 are now pending in the application. Reexamination and reconsideration of the claims is respectfully requested in view of these amendments and the following remarks.

The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Rejection of the Claims under 35 U.S.C. §112, First Paragraph, Written Description, Should Be Withdrawn

Claims 20-24, 26-38, and 40-44 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Claims 27 and 41 have been canceled. This rejection is respectfully traversed as applied to the remaining claims.

The amended claims are drawn to methods for treating non-Hodgkin's lymphoma in a human subject wherein the subject is administered human IL-2 or biologically active variant thereof, where the variant of human IL-2 has the ability to promote natural killer (NK) cell expansion and function and has at least 90% sequence identity to the amino acid sequence for human IL-2. Thus, the IL-2 variant for use in the claimed methods must structurally have at least 90% amino acid sequence identity to the sequence for human IL-2 and must have the function of being able to promote NK cell expansion and function.

The "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1, 'Written Description' Requirement" state that a genus may be described by "sufficient description of a representative number of species . . . or by disclosure of relevant, identifying

characteristics, i.e. structure or other physical and/or chemical properties." 66 Fed. Reg. 1106 (January 5, 2001). This is in accordance with the standard for written description set forth in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), where the court held that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, or chemical name' of the claimed subject matter sufficient to distinguish it from other materials." 119 F.3d at 1568, citing *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993).

The Federal Circuit has made it clear that sufficient written description requires simply the knowledge and level of skill in the art to permit one of skill to immediately envision the product claimed from the disclosure. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("One skilled in the art must immediately discern the limitations at issue in the claims."). The present claims recite a variant of human IL-2 that has at least 90% amino acid sequence identity to the sequence for human IL-2. Applicants respectfully note that the amino acid sequences for human IL-2 and numerous IL-2 variants were well known in the art at the time of the present invention, as were methods for recombinantly producing these proteins. See the specification, for example, at page 18, lines 16-28, citing to Taniguchi *et al.* (1983) *Nature* 302:305-310 and Devos (1983) *Nucleic Acids Research* 11:4307-4323 for production of native-sequence IL-2, and to Wang *et al.* (1984) *Science* 224:1431-1433 for production of mutationally altered IL-2, as well as to U.S. Patent Nos. 4,604,377, 4,738,927, 4,656,132, 4,569,790, 4,748,234, 4,530,787, 4,572,798, 4,748,234, and 4,931,543 (page 39, lines 26-27); and the extensive list of IL-2 muteins provided at page 18, line 30, continuing through page 19, line 12. Furthermore, the specification provides guidance as to how % sequence identity to human IL-2 is to be calculated, i.e., at pages 16-17, particularly lines 21-27 of page 16, stating the preferred ALIGN program and respective parameters that are to be used to calculate sequence identity.

Notably, Devos *et al.* (1983) *Nucleic Acids Res.* 11(13):4307-4323, provided herewith as Appendix A, at Figure 3 on page 4315, described the molecular cloning of this protein almost twenty years before the present application was filed; Clark *et al.* (1984) *Proc. Natl. Acad. Sci.* 81:2543-2547, provided herewith as Appendix B, at Figure 1 on page 2545, also presented the

amino acid sequence and coding sequence for this protein; and Schrader *et al.* (1986) *Proc. Natl. Acad. Sci.* 83:2458-2462, provided herewith as Appendix C, at Figure 2 on page 2460, described the structural similarity between IL-2 and other related cytokines. Therefore Applicants respectfully submit that one of skill in the art would view the recitation of a sequence having at least 90% amino acid sequence identity to the sequence for human IL-2 as a very predictable structural requirement encompassed by the human IL-2 variants to be used in the methods of the claimed invention.

Furthermore, as noted above, specific examples of human IL-2 variants are disclosed in the specification. See the disclosure at page 18, line 30, continuing through page 19, line 12, stating (emphasis added):

> For examples of variant IL-2 proteins, see European Patent Application No. **136,489**; European Patent Application No. 83101035.0 filed February 3, 1983 (published October 19, 1983 under Publication No. 91539); European Patent Application No. 82307036.2, filed December 22, 1982 (published September 14, 1983 under No. 88195); the recombinant IL-2 muteins described in **European Patent Application No. 83306221.9**, filed October 13, 1983 (published May 30, 1984 under No. 109748), which is the equivalent to Belgian Patent No. 893,016, commonly owned **U.S. Patent No. 4,518,584**; the muteins described in U.S. Patent No. **4,752,585** and **WO 99/60128**; and the IL-2 mutein (des-alanyl-1, serine-125 human interleukin-2) used in the examples herein and described in **U.S. Patent No. 4,931,543**, as well as the other IL-2 muteins described in this U.S. patent; all of which are herein incorporated by reference.

Applicants respectfully note that the patents and patent applications disclosed in the present specification (and denoted in bold in the excerpt above) describe no less than 43 variants of human IL-2 that were known in the art at the time of the present invention. See the expanded description provided in related and commonly owned U.S. Continuation-in-Part Application No. 10/293,664, filed November 12, 2002, and published as U.S. Patent Application Publication No. 2003-0185796. Paragraph 0087 at page 14 of this publication, recites each of these patents and patent applications and a listing of the variant human IL-2 polypeptides disclosed therein. As can be seen from this expanded listing in the copending application for each of the patents and

patent applications that were disclosed and thus taught in the present specification, variants of human IL-2 were well known in the art at the time of the present invention.

Applicants take this opportunity to remind the Examiner that a satisfactory disclosure of a "representative number" of species within a genus depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2000). Applicants submit that the knowledge and level of skill in the art would allow a person of ordinary skill to envision the human IL-2 variants recited in the claimed invention, i.e., human IL-2 variants that have at least 90% amino acid sequence identity to the amino acid sequence for human IL-2.

Applicants respectfully note that the description of a claimed genus can be by structure, formula, chemical name, or physical properties. See *Ex parte Maizel*, 27 USPQ2d 1662, 1669 (B.P.A.I. 1992), citing *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). The recitation of a predictable structure of a sequence having at least 90% amino acid sequence identity to the sequence for human IL-2 is sufficient to distinguish the claimed polypeptide sequences from other materials and thus sufficiently define the claimed genus. Thus, human IL-2 variants of the invention require structural conformity to the well-known polypeptide sequence of human IL-2, and are therefore adequately described to one of skill in the art.

Applicants have further provided the functional characteristic that distinguishes the claimed variant sequences. Specifically, the claims recite that the human IL-2 variants are capable of promoting NK cell expansion and function. Accordingly, both the structural properties and the functional properties that characterize the claimed genus are specifically recited in the claims.

This functional requirement can be tested using any routine assay for measuring NK cell expansion and function, including mediation of ADCC. As the specification notes, methods for assaying for NK cell expansion and function were well known in the art at the time of the present invention. See, for example, Morgan *et al.* (1976) *Science* 193:1007-1011, referred to on page 1, lines 23-24 of the specification (lines 6-7) article; as well as the numerous references cited in the

Information Disclosure Statements (IDS) filed by Applicants on September 10, 2001, November 9, 2001, and November 21, 2005. Therefore, human IL-2 variants that share the structural requirement of having at least 90% amino acid sequence identity to the sequence for human IL-2 but that do not share the functional requirement of having the ability to promote NK cell expansion and function are not encompassed by the claims.

Applicants have provided more than a mere statement that variants are part of the invention and reference to a method of isolating them. In this manner, Applicants have provided specific structural requirements of the variants being claimed, i.e., having at least 90% amino acid sequence identity to the sequence for human IL-2, which was well known in the art at the time of Applicants' invention. Furthermore, the claims recite a limitation requiring the human IL-2 variant to have a specific function, i.e., the ability to promote NK cell expansion and function).

Applicants have conveyed with reasonable clarity to one skilled in the art that they were in possession of the invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention (emphasis added). See, e.g., *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

In summary, contrary to the Examiner's conclusion, the skilled artisan could recognize which variants of IL-2 would satisfy the claimed structural limitation, and would be aware of

routine assays that could be used to measure the ability of the recited variants to promote NK cell expansion and function. Accordingly, the requirement under 35 U.S.C. §112, first paragraph, as it relates to the remaining pending claims has been satisfied, and therefore the written description rejection should be withdrawn.

The Rejection of the Claims under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 20-24, 26-38, and 40-44 are rejected under 35 U.S.C. §103(a) as being unpatentable over Grillo-Lopez *et al.* (U.S. Patent No. 6,455,043) in view of Halenbeck *et al.* (U.S. Patent No. 4,931,543; hereinafter referred to as "Halenbeck"). These claims are also rejected as being obvious over Grillo-Lopez *et al.* (WO 00/09160), the PCT application corresponding to the application that issued as U.S. Patent No. 6,455,043. In view of their same disclosure, and the Examiner's common grounds for rejection, these two obviousness rejections will be addressed together. Claims 27 and 41 have been canceled. This rejection is respectfully traversed as applied to the remaining claims.

Applicants respectfully submit that the previously presented claims were not obvious in view of the Grillo-Lopez *et al.* patent or WO publication for all of the reasons previously made of record. The fact that these references have been cited in combination with Halenbeck does not change Applicants' position, as Halenbeck merely teaches the IL-2 variant of claim 28.

Solely for the purposes of advancing prosecution, independent claims 20 and 31 have been amended to recite daily subcutaneous administration of a therapeutically effective dose of IL-2 or biologically active variant thereof, where the dose of this agent is in the range of 3 mIU/m^2 to 6 mIU/m^2. Thus, claims 20-24, and 26-35 all require that human IL-2 or biologically active variant thereof in the range of 3 mIU/m^2 to 6 mIU/m^2 is administered subcutaneously to a human subject **in combination with** administration of the anti-CD20 antibody or fragment thereof to treat non-Hodgkin's B-cell lymphoma. Applicants respectfully submit that neither the Grillo-Lopez *et al.* patent nor the companion WO publication teach or suggest the claimed administration protocol for treatment of non-Hodgkin's B-cell lymphoma.

The Examiner reasons that the disclosure at column 14, lines 48-60, of the Grillo-Lopez *et al.* patent teaches one of skill in the art to use a dose of 3 mIU/m^2 IL-2 in combination with an

anti-CD20 antibody therapy for treatment of non-Hodgkin's lymphoma. Applicants respectfully disagree. The paragraph that the Examiner refers to states:

> Lauria et al. (56) treated 11 patients with high grade NHL at a median of 42 days after ABMT with IL-2 at a dose of $2x10^6$ IU/m^2 qod for two weeks and then $3x10^6$ IU/m^2 **twice a week** for a year (emphasis added).

Thus, this IL-2 dose is taught for **single-agent therapy**, not combination therapy with IL-2 and an anti-CD20 antibody. The Examiner points to this dose, and reasons that Applicants' IL-2 dose of 4.5 mIU/m^2, as taught in Example 1, is close to the dose disclosed in the Grillo-Lopez *et al.* patent for treatment of non-Hodgkins' B-cell lymphoma (Office Action mailed May 4, 2007, at page 7, first paragraph).

However, Applicants respectfully note that the $3x10^6$ IU/m^2 dose of IL-2 taught by Lauria *et al.* for **single-agent therapy** is administered **twice a week**, for a **total weekly dose** of **6 $x10^6$ IU/m^2** (i.e., **6 mIU/m^2**). This is to be contrasted with Applicant's claimed invention set forth in claims 20-24, and 26-35, wherein $3x10^6$ IU/m^2 of IL-2 or variant thereof is administered **daily**, for a **total weekly dose** of **21 $x10^6$ IU/m^2** (i.e., **21 mIU/m^2**). Thus, a patient undergoing therapy in accordance with Applicants' claimed invention is receiving a total weekly dose of IL-2 or biologically active variant thereof that is at least **3.5-fold greater** than the total weekly dose of IL-2 that would be administered in accordance with the IL-2 dosing protocol that is taught by Lauria *et al.* for **single-agent therapy**. As for the 4.5 mIU/m^2 IL-2 dose referred to in Applicants' Example 1, this dose was administered 5 times per week, for a total weekly dose of IL-2 of **22.5 mIU/m2**. Again, this is not even close to the "low-dose IL-2" that Lauria *et al.* teach for **single-agent therapy**, and which the Examiner relies on as rendering obvious Applicants' claimed invention.

Furthermore, claims 31-44 of the present invention require **specific dosing regimens** for **both** the anti-CD20 antibody or antibody fragment **and** the IL-2 or biologically active variant thereof that are to be used **in combination** to treat non-Hodgkin's B-cell lymphoma. Thus, for claims 31-35, 40, and 42-44, antibody administration begins on day 1 of a treatment period, and

daily subcutaneous dosing of IL-2 or variant thereof begins within 7 days of antibody administration. For claims 36-38, antibody administration begins on day 1 of a treatment period, and three-times-a-week dosing of IL-2 or variant thereof begins on day 8 of this treatment period. These administration and dosing protocols are not taught or suggested by the Grillo-Lopez *et al.* patent or WO publication. In fact, these two cited references fail to teach or suggest **any protocol** for administering **combination therapy** with IL-2 and anti-CD20 antibody.

The Examiner submits that the effectiveness of the low IL-2 doses as taught by the cited Grillo-Lopez *et al.* references in pointing to Lauria *et al.* would have led one of skill in the art to use this low IL-2 dose in combination therapy with an anti-CD20 antibody to treat non-Hodgkin's B-cell lymphoma, and that one of skill in the art would have been motivated to do so given the statement in Grillo-Lopez that B-cell lymphomas can be treated by "administering a synergistic therapeutic combination comprising at least one anti-CD20 antibody and at least one cytokine, wherein the therapeutic effect is better than the additive effects of either therapy administered alone" (see Grillo-Lopez *et al.* patent at column 3, lines 27-32. Further, the Examiner submits that "[a] routineer would have determined the optimal schedule of administration using routine experimentation" (Office Action mailed May 4, 2007, at page 5, last paragraph). Applicants respectfully disagree for all of the reasons made of record and further in view of the following.

The Grillo-Lopez *et al.* patent and WO publication fail to provide the requisite guidance as to how to modify the IL-2 doses disclosed in these cited references, which are disclosed solely **for use in single-agent therapy**, to arrive at the presently claimed **daily subcutaneous** dosing range for IL-2 or variant thereof that is **to be used in combination** with anti-CD20 antibody therapy, which leads to a total weekly dose of IL-2 or variant thereof that is at least **3.5-fold greater** than the total weekly dose that would be administered according to the IL-2 dose and twice-a-week dosing schedule taught by Lauria *et al.* **for single-agent therapy**. There is no disclosure whatsoever as to what protocol or doses of these two agents should be administered in combination to effectively treat non-Hodgkin's B-cell lymphoma. Though these two cited references claim to provide a method for treating B-cell lymphomas by administering a "synergistic therapeutic combination comprising at least one anti-CD20 antibody and at least one

cytokine," they fail to disclose even one example of how one would achieve this objective. A mere statement that one can achieve a synergistic therapeutic effect with two different classes of drugs with no guidance whatsoever as to how to proceed to administer these two classes of drugs in combination to achieve a synergistic effect, much less an additive one, can hardly be interpreted as providing an enabling disclosure for achieving that synergistic therapeutic effect.

That being said, at most, the teachings of the Grillo-Lopez *et al.* patent and WO publication suggest that low-dose IL-2 and anti-CD20 antibody therapy could be used to treat B-cell lymphoma. Given the lack of guidance, these two cited references merely provide an invitation to experiment.

Yet an invitation to experiment is not sufficient grounds to reject an invention as obvious. It is well settled in the case law that in order to render a claimed invention obvious within the meaning of 103, the prior art must contain some suggestion of the desirability and the manner of making the proposed modification. See, e.g., *In re Antonie*, 559 F.2d 618, 195 USPQ 6; *In re Taborski*, 183 USPQ 50; and *In re Murch,* 175 USPQ 89. Moreover, the mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Laekowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989).

The Grillo-Lopez *et al.* patent and WO publication do not guide the skilled artisan to the recited anti-CD20/IL-2 combination therapy that Applicants have discovered is beneficial to treat non-Hodgkin's B-cell lymphoma. Rather, at most these two references teach that the very low doses of IL-2 relied on for this rejection (i.e., 3 mIU/m^2, 2 mIU/m^2, and 0.45 mIU/m^2) were efficacious for cancer treatment when administered in **single-agent therapy**. No guidance is provided as to how these low IL-2 doses should be modified for combination therapy with an anti-CD20 antibody to safely and efficaciously treat non-Hodgkin's B-cell lymphoma. The low doses of IL-2 taught by the Grillo-Lopez *et al.* patent and WO publication were not predictive of the higher IL-2 doses that Applicants' have discovered are efficacious in treatment of non-Hodgkin's lymphoma when administered subcutaneously in combination with an anti-CD20 antibody therapy.

Furthermore, the specific dosing regimens recited in independent claims 31 and 36, and

in claims dependent therefrom, is not suggested by these two cited references. The Grillo-Lopez *et al.* patent and WO publication provide no guidance whatsoever as to a dosing regimen to be used for combination therapy with IL-2 and anti-CD20 antibody. In the absence of such guidance, one of skill in the art is left with a myriad of possible dosing regimens to choose from, with no reasonable expectation of successfully modifying the teachings of these two cited references to arrive at Applicants' claimed invention. Again, this is at most an invitation to experiment, yet an invitation to experiment is not sufficient grounds to reject an invention as obvious.

Applicants provided post-filing evidence (Gluck *et al.* reference, submitted as Appendix A in the response filed May 5, 2005) that the Examiner has dismissed as not being related to the present invention. The Examiner contends that the teachings in Gluck *et al.* do not reflect the teachings in Applicants' specification. Applicants respectfully disagree.

Maurice Wolin, a joint inventor on the present application, was a contributing author on this article, which reports on the results of two parallel phase I clinical trials that were based on the doses and dosing regimens taught in the present application. In this manner, Applicants' specification teaches that patients having non-Hodgkin's B-cell lymphoma are treated with combination anti-CD20 and IL-2 therapy, where the IL-2 or variant thereof is administered by **daily subcutaneous** administration. The specific phase I clinical trial mentioned in Example 2 of the present invention states that patients with non-Hodgkin's lymphoma will participate in "[A]n open label, single arm study of escalating doses of IL-2 in combination with the labeled dose of Rituximab . . .. The Rituximab dose is fixed at 375 mg/m^2 while IL-2 is given in progressively increasing doses until the outpatient MTD is reached. Rituximab is given weekly beginning on week 1 and ending on day 1 of week 4. A daily dose of Proleukin is given starting in week 2 and continuing through week 5." See the specification at page 29, lines 20-26. The patients receive escalating doses of IL-2, as follows:

> The Rituximab dose is fixed at 375 mg/m^2 while IL-2 is given in progressively increasing doses until the outpatient MTD is reached. Rituximab is given weekly beginning on week 1 and ending on day 1 of week 4. A daily dose of Proleukin is given starting in week 2 and continuing through week 5. Patients remain on a

fixed dose of IL-2 throughout this period.

Specification at page 29, line 29, continuing through page 30, line 2. This example goes on to say the following:

> Patients are entered into groups of three. All receive Rituximab 375 mg/m^2 via 6 hr infusion starting on day 1 and then weekly for 4 weeks (i.e., on days 8, 15, and 22) per the labeled dose for the agent. Proleukin is started in week 2 (on day 8) at the prescribed dose level and given daily by subcutaneous injection for 4 weeks (i.e., through day 35 of the treatment period).

This example teaches that the doses to be administered subcutaneously on a daily basis are 2 x 10^6 IU, 4.5 x 10^6 IU, and 7.5 x 10^6 IU, i.e. 2 mIU, 4.5 MIU, and 7.5 MIU. See the table set forth on page 31 of the specification.

Applicants' further teach and claim an administration protocol to treat patients with non-Hodgkin's B-cell lymphoma, wherein the anti-CD20 antibody, such as Rituxan, is administered on day 1 of a treatment period, and on days 8, 15, and 22 of this treatment period, and thrice weekly dosing of IL-2 or variant thereof (for example, Proleukin) at a dose of 3 mIU/m^2 to 14 mIU/m^2 is administered beginning on day 8 of this treatment period and continuing for three weeks. See the specification at pages 11-12, teaching the doses of IL-2 or variant thereof, and at page 12, line 27, continuing through page 13, line 9, teaching the IL-2 dosing schedule, and claims 36-38.

Applicants respectfully submit that the teachings set forth in their specification, and the combination therapy recited in Applicants' claimed invention are reflected in the dosing protocols described for the NHL01 and NHL02 phase I clinical trials for non-Hodgkin's B-cell lymphoma patients that are reported on in the Gluck *et al.* reference. In this manner, Gluck *et al.* outline their study design and dosing as follows:

> Studies NHL01 and NHL02 were open-label Phase I trails evaluating escalating doses of IL-2 (aldesleukin; Proleukin), delivered either daily (NHL01) or thrice weekly (NHL02), in combination with a fixed dose of rituximab (Rituxan). The studies enrolled initial cohorts of 3 patients at each dose level . . .

Gluck *et al.* , at page 2254, column 2, "Study Design," lines 1-5. Gluck *et al.* teach that their protocol was as follows:

> In NHL01, patients received rituximab 375 mg/m^2 administered i.v. weekly for 4 consecutive weeks; starting at week 2, IL-2 was administered by s.c. injection for 4 consecutive weeks, at daily doses of 2, 4.5, 6, or 7.5 MIU, corresponding to cumulative weekly IL-2 doses 14, 31.5, 42, and 52.5 MIU per week, respectively. In NHL02, patients received rituximab 375 mg/m^2 administered i.v. weekly for 4 consecutive weeks, at doses of 4.5, 10, 14, or 18 MIU, corresponding to cumulative weekly IL-2 doses of 13.5, 30, 42, and 54 MIU per week, comparable with the cumulative weekly doses administered in NHL01.

Gluck *et al.*, at page 2254, column 2, "Treatment," lines 1-12. See also their treatment schemas shown in Figure 1. Applicants respectfully note that the doses referred to for thrice weekly dosing correspond to 2.65 mIU/m^2, 5.9 mIU/m^2, 8.2 mIU/m^2, and 10.6 mIU/m^2, all of which fall within the range of 2 mIU/m^2 to 12 mIU/m^2 disclosed by Applicants. See the specification at page 11, line 24.

Thus, contrary to the Examiner's position, Applicants submit that the post-filing data published as Gluck *et al.* is reflective of Applicants' claimed methods for treating non-Hodgkin's lymphoma, and therefore is admissible to support Applicants' position that a *prima facie* case of obviousness has not been established.

Applicants' have discovered what was not taught or suggested by the Grillo-Lopez *et al.* patent and WO publication, i.e., that IL-2 administered subcutaneously to non-Hodgkin's B-cell lymphoma patients according to the claimed administration protocols and claimed dosage ranges provides for efficacy of treatment with IL-2/anti-CD20 antibody therapy. Further, Applicants have discovered that IL-2 administration frequency can advantageously be decreased from daily to thrice-weekly dosing to provide for superior therapeutic results with IL-2/anti-CD20 antibody therapy in these patients.

The fact that the secondary reference, Halenback, teaches the IL-2 variant recited in claim 28, provides no further guidance as to how IL-2 or a biologically active variant thereof

should be administered in combination with an anti-CD20 antibody to safely and efficaciously treat non-Hodgkin's B-cell lymphoma.

As the Examiner is aware, establishing a *prima facie* case of obviousness requires assessment of the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), which provides the framework for applying the statutory language of §103. Under the "Graham Factors," the Examiner is required to:

1. Determine the scope and content of the prior art;
2. Ascertain the differences between the prior art and the claims at issue;
3. Resolve the level of ordinary skill in the pertinent art; and
4. Consider any relevant secondary considerations.

Furthermore, a *prima facie* case of obviousness under 35 U.S.C. § 103(a) requires that the combination of references places the claimed subject matter in the public domain prior to Applicants' date of invention. See *In re Zenitz*, 333 F.2d 924, 142 USPQ 158 (C.C.P.A. 1964). Thus, establishing a *prima facie* case of obvious requires that the cited references can be combined such that each and every element of the claimed invention is taught, explicitly or implicitly, by the references and that a reasonable expectation of success exists in such a combination. In the instant case, the Grillo-Lopez *et al.* patent and its corresponding WO publication, by themselves or in combination with Halenback, fail to teach or suggest the IL-2 doses and administration protocols for combination therapy with an anti-CD20 antibody to treat non-Hodgkin's B-cell lymphoma in the manner set forth in Applicants' claimed invention.

Furthermore, at the most, the Grillo-Lopez patent and its companion WO publication generically suggest combination therapy with anti-CD20 antibody and IL-2, leaving one of skill in the art with an invitation to experiment with many possible avenues of approach to try to achieve the desirable result, i.e., treatment of non-Hodgkin's B-cell lymphoma using this combination therapy. They do not provide enough guidance to form a reasonable expectation that the process as utilized by Applicants here would actually succeed. Where the prior art gives only general guidance as to the particular form of the invention or how to achieve it, as here, obviousness may not be found. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81, 90-91 (Fed. Cir. 1986).

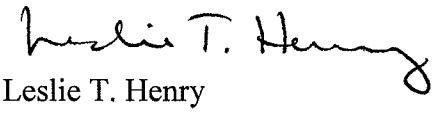
Accordingly, Applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §103(a) and §112, first paragraph, are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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